Statistical Bases for Defining Level of Assurance

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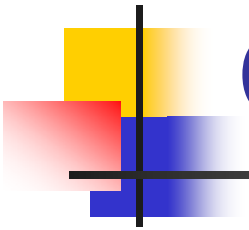


Outline

- Assurance versus control
- Bases for assurance
- Risks associated with assurance
- Risk analysis

Assurance versus Control

- ***Assurance:*** The act of assuring; a declaration tending to inspire full confidence; that which is designed to give confidence (*Webster's Revised Unabridged Dictionary*)
  - Usually associated with carefully planned experiments, that demonstrate “elimination” of risk from the process.
- ***Quality Control:*** The assessment of product compliance with stated requirements.
  - Usually associated with periodic testing, batch to batch or over time.

Bases for Assurance

- ***Customer defined cutoff***
  - ***Dose exposure studies in animals***
    - ***Strength:*** carefully controlled experiment allowing an unambiguous conclusion
    - ***Weakness:*** appropriateness of animal model
  - ***Observational study in humans***
    - ***Strength:*** direct impact on human subjects
    - ***Weakness:*** no control over level of exposure

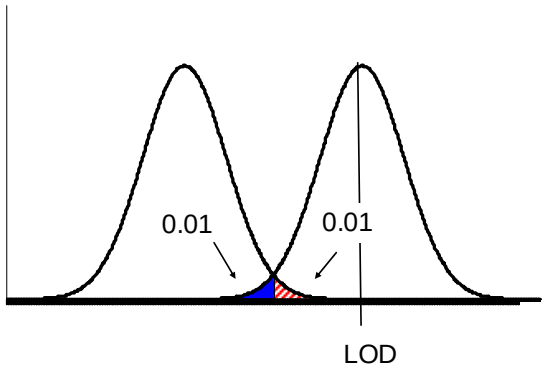
Bases for Assurance

- ***Analytically defined cutoff***
  - ***Defined by limit of detection of assay***
    - ***Strength:*** carefully conceived validation yields unambiguous level of detection
    - ***Weakness:*** detection level subject to sensitivity of technology
  - ***Probability of detection at low concentrations***
    - Detectability subject to sampling

Analytically Defined Cutoff

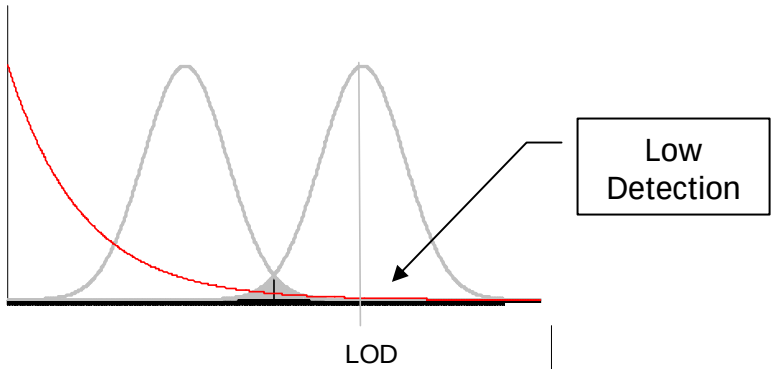
- Usually determined as level that can be detected reproducibly
  - Design: titrate organism down to low levels, in several runs of the assay
  - Analysis: determine level that can be reproducibly detected (eg., 95% of the time)
  - Issue: new technologies have lower levels of detection; in fact different laboratories using the same technology might have a different level of detection

Analytically Defined Cutoff

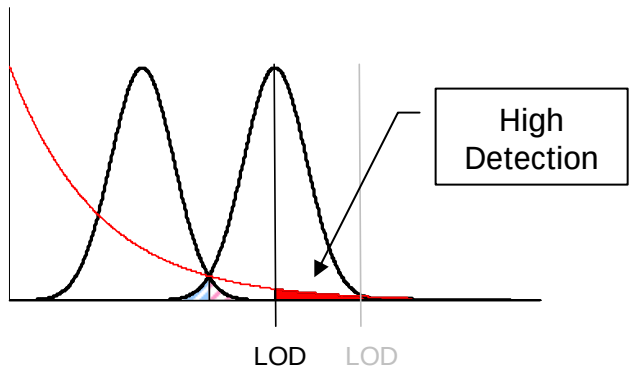


- LOD determined as level with high probability of detection (low risk of non-detection)

- Distribution of load yields no detection by classical procedure.



- New technology has lower LOD, yielding detects in product distribution

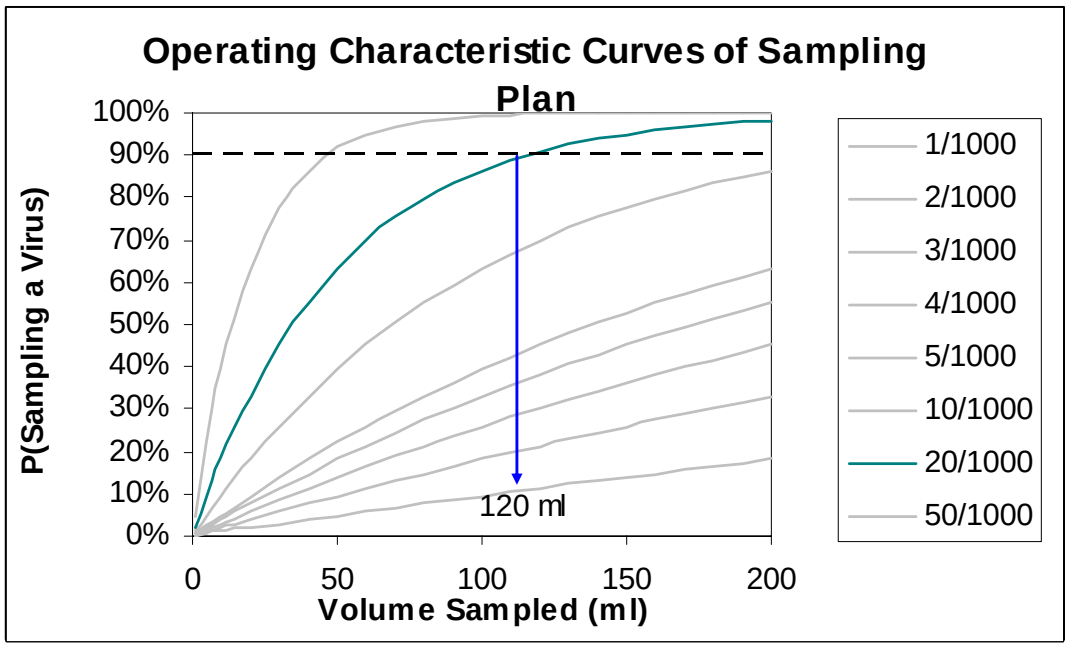


Analytically Defined Cutoff

- Question 1: should same cutoff be used with new detection technology?
  - Requires determination of LOD of old technology
- Question 2: what test design should be used to qualify materials in the new assay?
  - Should the new procedure be quantitative, yielding measurements that can be compared to the cutoff?
  - Or can a single “calibration” sample be used, at the cutoff?

Probability of Detection

- Poisson sampling



$$p = \left(\frac{V - v}{V}\right)^n, [C] = \frac{n}{V}$$

approximated by

$$p = e^{-c \cdot v}, \text{ where}$$

$c = [C]$ per liter

$v =$ sampled volume

Probability of Detection

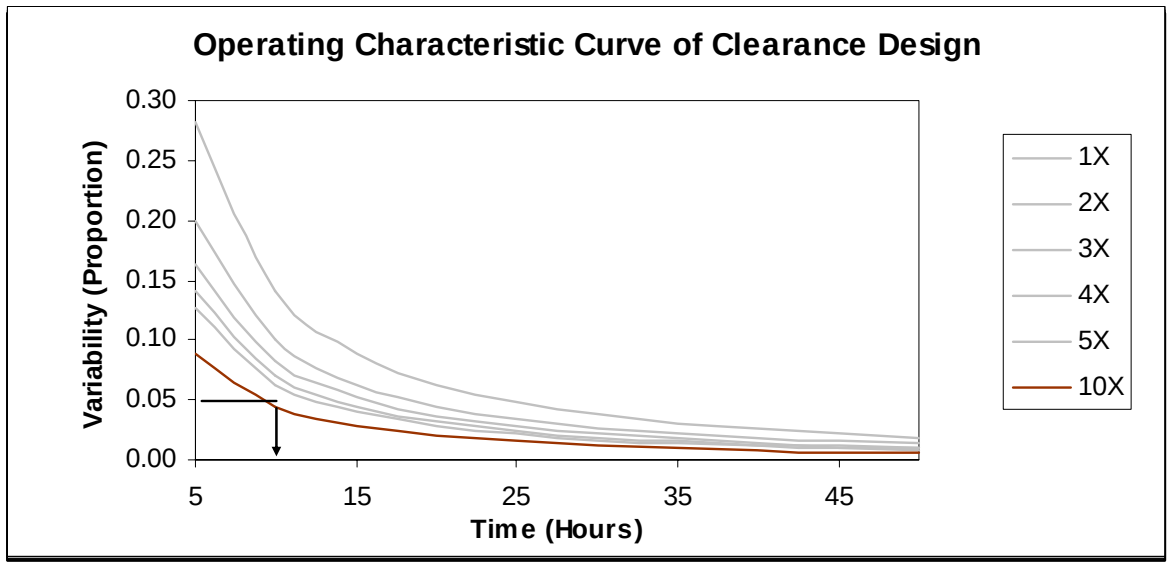
- Sampling should ideally be dictated by the desire to detect a “meaningful” level
- Such tests might be better viewed as precautionary

Bases for Assurance

- ***Clearance study***
  - ***Strength:*** carefully controlled experiment showing reproducible clearance of expected contaminant
  - ***Weakness:*** can not show “complete” clearance since most clearance curves are logarithmic

Clearance Study

- Study design
  - Design dictates precision of estimate of clearance rate



Clearance Study

- Choice of design
  - Clearance factor (“x”) affected by input microbial potency and limit of detection of assay
  - Replication and range in “x” reduces variability
    - Reduce to a “desirable” level
    - Reduce to a level of “diminishing returns”

$$\text{Margin of Error} = 2 \cdot \text{Sigma} = 2 \cdot \sqrt{\frac{s^2}{n \cdot (t-1) \cdot \text{var}(x)}}$$

Risk Analysis

- Like clearance study, consider reduction factors

$$\text{Reduction} = F_1 \cdot F_2 \cdots F_k$$

$$\log(\text{Reduction}) = \log(F_1) + \log(F_2) + \cdots \log(F_k)$$

$$\text{Var}(LR) = \sum \text{Var}\left[\log(F_i)\right]$$

$$CI = LR \pm z \cdot \sqrt{\text{Var}(LR)}$$

Summary

- Detectable level in a sample is affected by LOD and sample volume.
- A desirable level of load should be established, then the procedure designed to detect this level.
- QC is precautionary, while QA provides greater assurance of reduction to a desirable level.

Summary (cont.)

- Depending on the specific concern, its likelihood, the impact of the concern actually occurring, and the technology, one may chose to do QC or QA or a combination of the two.
- One size does not fit all occasions, and a variety of approaches is typically needed across a family of products.